"therapeutically effective amount" is defined in regard to inhibiting cell growth or proliferation. Additionally, on page 49, line 27 through page 50, line 2 of the specification it states "[d]etermination of the effective amounts is well within the capability of those of ordinary skill in the art, especially in light of the detailed disclosure provided herein." Therefore, the term "therapeutically effective amount" would not be considered unclear by a person of ordinary skill in the art.

The examiner also asserts that the term "agent" in claims 26-35 is not clear. Applicants respectfully disagree and direct the examiner's attention to page 6, lines 7-9 where therapeutic agents are described as "agents able to modulate APB mediated activity between proteins and, thus alter signal transduction." Further, agents are described on page 10, lines 3-15, particularly in lines 12-15. Additionally, applicants direct the examiner attention to page 23, line 26 through page 33, line 7 where the agents encompassed by the present invention and methods for identifying such agents are described. Further, the claim recites that the agent decreases the binding between an APB recognition and an APB domain. Therefore, the term "agent" would not be considered unclear by a person of ordinary skill in the art.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 26-35 are rejected by the examiner under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Applicants respectfully request reconsideration and withdrawal of the rejection.

A. On page 3, paragraph 5 of the outstanding office action, the examiner asserts that the term "APB domain" encompasses a large number of proteins, as APB domain is broadly defined in the specification as having at least 20% sequence identity to the APB domain present in Shc. Applicants have amended claim 26 to recite "wherein said APB domain shares at least 80% sequence similarity or at least 75% sequence identity with the APB domain present in Shc." Support for this amendment is found in the present specification on page 25, lines 1-6.

The method of amended claim 26 is enabled because a person of ordinary skill in the art would be able to identify an APB domain that shares at least 80% sequence similarity or at least 75% sequence identity with the APB domain present in Shc using techniques readily available to those of skill in the art. Addiitionally, the specification discloses the amino acid sequence of a polypeptide that comprises an APB binding domain (see Figure 1) and this polypeptide sequence is claimed in the parent application, now U.S. 5,807,989.

B. On page 6, paragraph one of the outstanding office action, the examiner asserts that no other APB recognition regions are taught or suggested, other than the exemplified EGFR, HER2/neu and TrkA. Applicants respectfully disagree. The APB domain has been identified as part of a known protein, Shc, and thus, other proteins having this domain can be readily identified by one of ordinary skill in the art. Therefore, the present specification does teach and suggest molecules containing an APB recognition region, other than the exemplified EGFR, HER2/neu and TrkA.

C. On page 6, paragraph 1 of the outstanding office action, the examiner asserts that since no agent is administered, it is not clear how any agent would affect binding between an APB domain and an APB recognition region. Applicants respectfully disagree and direct the examiner's attention to a heading entitled "Identification of APB Modulating or Binding Agents" on page 29, line 16 of the specification. It is submitted that this section is highly probative of enablement and directly refutes the examiner's contentions. This section describes affinity binding methods wherein an APB domain containing protein is exposed to various potential binding agents and those showing binding affinity are isolated and characterized according to routine methods in the art. For example, on page 31, lines 3-9 of the specification it states:

> *Molecules exhibiting binding activity may be further screened for an ability to effect APB binding or modulate APB mediated activity. For example, the molecule can be tested for its ability to increase or decrease APB binding. Alternatively, the molecule may be tested for its ability to increase or decrease one or more activities mediated by the APB domain protein.*

The specification continues with a discussion of alternative assays that can be used to identify compounds that can be used in the methods of the invention. Such assays include *in vitro* complex formation (page 31, line 12) and co-immunoprecipitation techniques well known to those of ordinary skill in the art (page 31, lines 24-25). Additional details are found on page 32, lines 7 et seq. wherein detailed methodologies that may be employed with the invention to confirm that the invention is enabled are disclosed.

Because the methods of the invention can take many forms including using therapeutic peptides, there is further discussion, beginning page 34 and again on page 52, of gene therapy techniques that can be employed using peptides that display activity against APB domain containing proteins.

Beginning on page 44, line 16 is a further section entitled "Diagnosis." This section continues through line 5 of page 46 and describes how protein complexes involving APB binding may be utilized in the prognostic evaluation of the condition of a patient suspected of exhibiting an APB affiliated signal transduction disorder.

On page 46, line 7 is a section entitled "Administration." This section describes how agents that modulate APB activity can be administered to a patient using standard techniques such as determining the LD_{50} and the ED_{50}. Page 47, line 17 et seq. describes how one of skill in the art possessed with knowledge such as found in Fingi et al. (1975) "The Pharmacological Basis of Therapeutics," Chapter 1, can put to use the invention for treatment. And, again, on page 48, line 11 is stated that resort may be had to "Remington's Pharmaceutical Sciences," 1990, 18th ed. Mack Publishing Co., Easton, PA, for various routes and modes of administration. See, e.g., page 52, line 8. Remington's is an extremely thorough and well-respected treatise on pharmaceutical formulations.

D. On page 6, paragraph 2 of the outstanding office action, the examiner asserts that sufficient evidence is not provided to support a role for APB binding in the mediation of signal transduction. Applicants respectfully disagree. The present invention concerns a

domain in the amino terminus of Shc that is implicated in tyrosine kinase-mediated signal transduction. The domain is distinct from the SH2 domain and represents a newly elucidated mechanism of protein interaction with growth factor receptors and other tyrosine-phosphorylated proteins. This amino terminal domain is shown to cooperate with the SH2 domain to promote binding to growth factor receptors. The nature of the invention thus has importance in signal transduction, particularly tyrosine kinase systems, and specifically in modulating signal transduction of such systems.

E. On page 7, paragraph 1 of the outstanding office action, the examiner asserts that the claims encompass the experimental and unpredictable field of in vivo therapy for mammals. The examiner asserts that in vitro tests are not sufficient to enable in vivo treatments. Applicants respectfully disagree and request reconsideration and withdrawal of the rejection.

The present specification provides sufficient enablement for the present method, as amended. It is well known in the art that molecules that disrupt the RAS-MAPK pathway are useful for treating cancer. The specification, at page 23, lines 10-25, identifies the binding of the APB domain of Shc to GRB2/SOS in the activation of the RAS pathway. In addition, as discussed in the left panel on page 231 of Luschnig, et al. *Molecular Cell* **5** 231-241 (2000), attached herewith as Exhibit 1, receptor tyrosine kinases activate the RAS-MAPK pathway. Luschnig et al. also state that mammalian SHC acts as an adaptor to link receptor tyrosine kinases via GRB2 to RAS activation (see page 231, right panel). Since molecules that disrupt the RAS-MAPK pathway are known to be useful for treating cancer, agents that decrease the binding between the APB binding domain of SHC and the APB recognition region of a protein that binds to SHC, should be useful for treating cancer. Therefore, the *in vitro* assay provided in the present specification is a good predictor of compounds that would be useful in the treatment of cancer. The examiner is respectfully referred to the Court of Appeals for the Federal Circuit's decision *in In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications.

It is noted that in the outstanding Office Action, the examiner raises specific "clinical" concerns with respect to the suitability of using the present method *in vivo*. Applicants assert that these types of concerns are more properly addressed by other government bodies, such as the FDA, and are therefore outside of the scope of the USPTO. The present application meets the USPTO's requirements for enablement. The clinical suitability of the present method for use *in vivo* is a question to be addressed by government bodies other than the USPTO. The present examples illustrate binding between an APB recognition region present in a first protein and an APB domain present in a second protein. As discussed above, when this binding is disrupted, the signal transduction pathway is disrupted, making this binding interaction a useful target for cancer therapy. Therefore, the present specification provides sufficient enablement for the presently claimed method.

The above discussion illustrates that the present specification provides enablement for the presently claimed method for altering signal transduction in an APB domain-containing signal transduction pathway. Therefore, the present claims comply with the requirements of 35 U.S.C. § 112, first paragraph.

CONCLUSION

As the above-presented amendments and remarks address and overcome all of the rejections presented by the Examiner, withdrawal of the rejections and allowance of the claims are respectfully requested.

If the Examiner has any questions concerning this application, he or she is requested to contact the undersigned.

Respectfully submitted,

Date March 25, 2002

By _____

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

26. (Amended) A method for altering signal transduction in an APB domain-containing signal transduction pathway comprising administering to a patient a therapeutically effective amount of an agent which decreases binding between an APB recognition region present in a first protein and an APB domain present in a second protein, wherein said APB domain shares at least 80% sequence similarity or at least 75% sequence identity with the APB domain present in Shc.